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OFFICE OF
PREVENTION, PESTICIDES AND
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MEMORANDUM

SUBJECT: DEET: Review of the supplemental data for upgrading two toxicology studies

Caswell No. 346 **DP Barcode**: D236426
PC Code. 080301 **Submission No.** S524768
MRID No. 44279901, 44279902, & 44279903

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The registrant, DEET Joint Venture, submitted data (a dose-range finding developmental toxicity study in rabbits) to upgrade a developmental toxicity study in rabbits and provided the missing information for a 90-day renal toxicity study in multiple strains of rats. This reviewer evaluated the currently submitted data. The conclusions are as follows:

a. Goldenthal, E.I. (1992). Evaluation of DEET in a multistrain 90-day dietary renal toxicity study in rats. International Research and development Corp.; Study No. 555-022, Oct 4,1992; MRID No. 42518101.

The objective of this study was to explore if there is an association between the renal toxicity seen in DEET treated male rats and the α_{2u}-globulin mechanism of renal toxicity. In this study, Groups of CD^R, Fischer, and NBR male rats (10/group) received either control diet or DEET treated diet at a concentration which would lead to a dose level of 400 mg/kg/day for 90 days.

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The results indicated that in CD^R male rats, DEET treatment produced an increased incidence of hyaline droplets in the renal tubules, renal tubular regeneration, chronic inflammation in the renal cortex, and granular casts in the renal tubules. In Fischer rats, hyaline droplet formation was seen in both the controls and DEET treated animals; renal toxicity was not affected by DEET treatment. In NBR rats, DEET did not produce any of the renal effects, which were seen in CD^R rats.

Previously, this study was classified as **Unacceptable** (Tox. Doc. 010528) because there are conflicting information on the actual dose. In addition, whether or not the findings of renal tubular dilation and tubular cell necrosis were seen are not reported.

Currently, the registrant submitted the missing data, which was reviewed and considered to be sufficient to fulfill the missing information. The supplemental data (MRID 44279901) showed that actual dose was 400 mg/kg body weight/day and the findings of renal tubular dilation and tubular necrosis were not seen in this study. This study is upgraded to be **Acceptable/Non-Guideline**.

b. Chun, J.S. and Neeper-Bradley, T.U. (1991). Developmental toxicity evaluation of DEET administered by gavage to New Zealand white rabbits. Bushy Run Research Center; Study No. 54-597. Dec 6,1991; MRID 42141101.

This study was previously reviewed and classified as **supplementary** because neither maternal nor developmental toxicities were seen in the highest dose tested, and the report failed to present an explanation for dose selection. In this study, the presumed pregnant rabbits received DEET by gavage at dose levels of 0, 30, 100, or 325 mg/kg/day from gestation days 6 to 18 (Tox. Doc. No. 009470). Currently submitted supplemental data consists of a dose-range finding developmental toxicity study in rabbits (MRID 44279903)[1] and an explanation for the dose selection including the rationale for upgrading this study (MRID 44279902).

Since the submitted study is a dose-range finding study (MRID 44279903), a Data Evaluation Report (DER) was not prepared. However, the relevant information is captured in the following summary.

In the dose-range finding developmental toxicity study, groups of "timed-pregnant" NZ white rabbits (5/dose group) received DEET (98.7%) by gavage at dose levels of 0 (corn oil), 62.5, 125, 250, 500, or 1000 mg/kg/day from gestation days 6 through 18. On gestation day 29, all the surviving does under went cesarean section and sacrificed. The fetuses were removed, weighed, and examined externally. The does were necropsied and examined for any treatment-related effects.

The results indicated that at doses of 250 mg/kg/day or above there was a non-dose-related increase in the incidence of rapid respiration (250 mg/kg/day, 3/5; 500 mg/kg/day, 2/5; 1000 mg/kg/day, 4/5) in the maternal animals. The incidence seen in 250 and 1000 mg/kg/day were statistically significant ($p<0.05$ & 0.01, respectively). At 1000 mg/kg, clinical signs of hypoactivity (3/5), ataxia (2/5), and prostration (1/5) were also seen.

Deaths were found in 500 and 1000 mg/kg/day groups (2/5 & 4/5, respectively). In 1000 mg/kg/day group, 2/5 animals died by day 9, and only 1 doe survived by day 12. The individual necropsy data showed that the animals that died at 500 and 1000 mg/kg/day groups all had sloughing and/or ulceration of the stomach lining. In contrast, the survivors did not show any gross pathology of the stomach. At doses of 500 mg/kg and above, the corrosive effect of DEET to the gastric lining appeared to be linked to the death of these animals.

Significant body weight losses were seen in 500 and 1000 mg/kg/day groups on gestation days 6-9, and large post-dosing rebounds in body weight were observed in the surviving does of these dose levels. However, mean maternal body weights were not significantly different among the test groups.

Food consumption was not affected by treatment at dose levels of 250 mg/kg or less. Food consumption was reduced at 1000 mg/kg/day; at 500 mg/kg/day reduced food intake occurred between gestation days 6 to 15.

At the time of cesarean section, viable fetuses were noted in all does (5/5) of the Control, 62.5, and 125 mg/kg/day groups. The number of does with viable fetuses in the 250, 500, and 1000 mg/kg/day groups were 4/5, 3/5, and 1/5, respectively. No evidence of treatment-related developmental toxicity was reported in any treatment groups. In the surviving litters, there was no evidence of pre- or post-implantation loss in treated groups as compared to the controls. Mean fetal body weights were generally increased as compared to the controls, even in the 3 surviving litters at 500 mg/kg/day and the one surviving litter at 1000 mg/kg/day. One fetus with gastroschisis was observed at 500 mg/kg/day, but this isolated malformation was not attributed to treatment.

Based on these results, the investigator of the study recommended 0, 30, 100, and 325 mg/kg/day be employed for the definitive developmental toxicity study in rabbits.

The results of the definitive study (MRID 42141101), in which no maternal nor developmental toxicity was observed at doses of ≤325 mg/kg/day were consistent with the results of the dose range-finding study, in which toxic effect was not seen in animals which were treated at doses below 500 mg/kg/day. In reviewing the definitive and the dose range-finding developmental toxicity studies together, the results indicate that the highest possible dose, which would not result in stomach ulceration and death for a gavage developmental toxicity study in rabbits, would probably be approximately 400 mg/kg/day.

The difference between 400 mg/kg/day and 325 mg/kg/day in a toxicological study is not marked. In the opinion of this reviewer, the highest dose tested in the definitive rabbit developmental toxicity study (325 mg/kg/day) has been adequately high to assess the maternal and the developmental toxicity of DEET. Little would be gained by conducting an additional study to establish a more precise NOEL and LEL, especially in light of the severe maternal toxicity noted at 500 mg/kg/day and above in the dose range-finding study. Therefore, the developmental toxicity study in rabbits (MRID 42141101) should be upgraded to **Acceptable.** The Executive Summary of the definitive study should make note of the results of the dose range-finding study (MRID 44279903), indicating that a maternal LEL was established at 500 mg/kg/day, while a developmental LEL which is not compromised by maternal toxicity appeared to be >500 mg/kg/day.

1. Neeper-Bradley, T.L. (1992). Developmental toxicity dose range-finding study of DEET administered by gavage to New Zealand white rabbits. Bushy Run Research Center (BRRC); Study No. 54-580. May 1, 1992. MRID 44279903. Unpublished.